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Subsequent pregnancy outcome after previous foetal death

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ABSTRACT

Objective: A history of foetal death is a risk factor for complications and foetal death in subsequent pregnancies as most previous risk factors remain present and an underlying cause of death may recur. The purpose of this study was to evaluate subsequent pregnancy outcome after foetal death and to compare cases of recurrent foetal death.

Study design: A retrospective cohort study in a tertiary referral centre. All women with a stillbirth beyond 16 weeks of gestation between January 1999 and December 2004 (n = 193) were identified. After providing informed consent, the medical records of 163 women were reviewed until August 2006 in terms of clinical, medical, obstetric and paediatric data of the pregnancy after the index pregnancy that resulted in foetal death. The cause of death for reported cases of foetal death and recurrent foetal death were classified by a multidisciplinary team according to the Tulip classification.

Results: Recurrent foetal death occurred in 11 cases, and various causes were identified. The cause of death was explained in seven cases. An association was found between the index foetal death and subsequent foetal death in some cases, especially in early gestation.

Conclusions: This study illustrates the importance of classifying the cause of recurrent foetal death and contributing risk factors using the same classification system. This provides more insight into the pathophysiological pathways leading to foetal death, and enables meaningful comparisons to be made in recurrent foetal death. This is required before preventive strategies can be instituted and implemented to reduce the risk of foetal death.

1. Introduction

Determination of risk factors and the cause of foetal death contributes to counselling and the management of future pregnancies, although the possibilities for intervention are limited, predominantly consisting of increased maternal and foetal surveillance, extra diagnostic tests and induction of labour near or at term. Due to underlying causes and pre-existing risk factors, a history of foetal death is a risk factor for complications and foetal death in subsequent pregnancies [1–9]. Studies have reported increased risk of recurrence ranging from 0 to 20-fold [1,10–14]. This risk depends on various characteristics of the index foetal death, including aetiology. The cause of death is often not described clearly in studies on recurrent foetal death, in either the index pregnancy or the subsequent pregnancy with an adverse outcome. As such, tailored management based on cause-specific recurrence of foetal death is often not possible. The purpose of this study was to evaluate pregnancy outcome after foetal death with a known cause classified according to the Tulip classification [15], and to describe the relationship with the cause of death in the case of recurrent foetal death.

2. Materials and methods

At the authors' tertiary centre, all cases of foetal death beyond 16 weeks of gestation are registered in a validated perinatal database. A case record form is completed that includes baseline characteristics such as date of delivery, gestational age, medical and obstetric history, maternal characteristics, foetal characteristics including foetal weight at birth, pregnancy details, and diagnostic test results including pathological findings from autopsy and placental investigation. Cause of death and risk factors involved in cases of foetal death are classified by a multidisciplinary team according to the Tulip classification; a system used to determine the cause and mechanism of perinatal death. This system consists of six main causes of death: congenital anomaly, placenta (placental bed pathology, placental pathology, umbilical cord complications), prematurity/immaturity [preterm

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prelabour rupture of membranes (PPROM), preterm labour], infection, other (foetal hydrops, maternal diseases, trauma, out of the ordinary) and unknown (despite thorough investigation, important information missing). Only one cause of death is allocated. Risk factors are defined as other known contributing factors on the causal pathway to death [15].

For this retrospective cohort study, women with a foetal death beyond 16 weeks of gestation between January 1999 and December 2004 were identified from the perinatal database. The cases identified are termed the 'index pregnancies'. All women lived in the north of the Netherlands and had full access to medical care. In 2005, the study group returned a self-completed questionnaire about their obstetric history after their index pregnancy. In addition, medical records were reviewed until August 2006 to collect clinical obstetric and paediatric data for the first pregnancy after the index pregnancy. Information acquired from medical records included medical history after the previous stillbirth, lifestyle characteristics, prenatal care, delivery and infant outcomes. Obstetric and medical history of the mother included age (at the beginning of the pregnancy), parity and current maternal diseases. Intra-uterine growth restriction (IUGR) was defined as birth weight below the 10th percentile of the Amsterdam birthweight chart [16]. Body mass index (BMI) greater than or equal to 30 kg/m^2 was defined as obesity.

Pregnancy outcomes after the index pregnancy were categorized as miscarriage before 16 weeks of gestation, foetal death between 16 and 22 weeks of gestation, foetal death beyond 22 weeks of gestation, neonatal death and a living child 28 days after birth. Neonatal death was defined as the death of a live-born child before 28 days of age. Abstaining from pregnancy was also registered. For all cases, gestational age at delivery was based on early ultrasound and the last menstrual period. Cause of foetal death in subsequent pregnancies was classified similarly to index pregnancies.

Data were analyzed using Statistical Package for the Social Sciences Version 14.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as means, and categorical variables are expressed as frequencies and percentages. Ninety-five percent confidence intervals were computed if appropriate. The study was approved by the Medical Ethics Committee of the University Medical Centre Groningen, and all women gave informed consent.

Table 1
Cause of death in the index pregnancy classified according to the Tulip classification ($n = 163$).

Cause of death	*n* (% of total)	Subclassification		*n*
Congenital anomaly	25 (15.3%)	Chromosomal defect	Numerical	13
			Structural	2
		Heart and circulatory system		4
		Neoplasm		2
		Other	Multiple organ	4
Placenta	78 (47.8%)	Placental bed pathology		53
		Placental pathology	Development	15
			Parenchyma	6
		Umbilical cord complication		2
		Not otherwise specified		2
Prematurity/immaturity	14 (8.6%)	Preterm prelabour rupture of membranes		9
		Preterm labour		3
		Cervical incompetence		2
Infection	4 (2.5%)	Transplacental		2
		Ascending		2
Other	7 (4.3%)	Foetal hydrops of unknown origin		4
		Maternal disease		2
		Out of the ordinary		1
Unknown	35 (21.5%)	Despite thorough investigation		12
		Important information missing		23
Total	163 (100%)			

Table 2
Pregnancy outcome after the index pregnancy ($n = 163$) by cause of death in the index pregnancy.

	Total		Cause of death in the index pregnancy according to Tulip classification											
			Congenital anomaly		Placenta		Prematurity/ immaturity		Infection		Other		Unknown	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Obstetric outcome														
Total (*n* = number of women)	163	100.0	24	100.0	79	100.0	14	100.0	4	100.0	7	100.0	35	100.0
No pregnancy	28	17.2	3	12.5	13	16.5	2	14.3	2	50.0	0	0	8	22.9
Miscarriage before 16 weeks	16	9.8	2	8.3	8	10.1	1	7.1	0	0.0	2	28.6	3	8.5
Ongoing single pregnancy after 16 weeks	113	69.3	17	70.8	54	68.3	11	78.6	2	50.0	5	71.4	24	68.6
Ongoing twin pregnancy after 16 weeks	6	3.7	2	8.3	4	5.1	0	0.0	0	0.0	0	0.0	0	0.0
Outcome ongoing pregnancies after index														
Total (*n* = number of children)	125	100.0	21	100.0	62	100.0	11	100.0	2	100.0	5	100.0	24	100.0
Foetal death between 17 and 22 weeks	7	5.6	0	0.0	2	3.2	2	18.2	0	0.0	0	0.0	3	12.5
Foetal death after 22 weeks	5	4.0	0	0.0	3	4.9	1	9.1	0	0.0	0	0.0	1	4.2
Neonatal death (before 28 days of age)	0	0	0	0.0	0	0	0	0	0	0.0	0	0.0	0	0.0
Living child (at 28 days)	113	90.4	21	100.0	57	91.9	8	72.7	2	100.0	5	100.0	20	83.3

Table 3
Recurrent foetal death after explained cause of death in the index pregnancy classified according to the Tulip classification.

Index pregnancy		Subsequent pregnancy	
Case 1			
Mother: 27 years of age, G8P3-1A4, 28 weeks of gestation, girl, 912 g, died in utero		Mother: 30 years of age, G9P3-2A4, 33 weeks of gestation, boy, 1790 g, died in utero	
Cause of death	Placenta; placental bed pathology: placental abruption	Cause of death	Placenta; placental bed pathology: placental abruption
Contributing factors	Smoking (10 cigarettes/day), congenital anomaly (neural tube defect)	Contributing factor	Smoking (10 cigarettes/day)
Comorbidities	Asthma, protein C deficiency, heterozygous factor V Leiden mutation	Comorbidities	Asthma, protein c deficiency, heterozygous factor V Leiden mutation
Case 2			
Mother: 20 years of age, G3P0A2, 28 weeks of gestation, boy, 550 g, died in utero		Mother: 21 years of age, G4P1-1A2, 21 weeks of gestation, boy, 130 g, died in utero	
Cause of death	Placenta; placental pathology; parenchyma: massive perivillous fibrin deposition	Cause of death	Placenta; placental pathology; parenchyma: massive perivillous fibrin deposition
Contributing factors	Scleroderma, IUGR, oligohydramnion	Contributing factors	Scleroderma, IUGR
Comorbidities	Mitral stenosis and mitral insufficiency	Comorbidities	Mitral stenosis and mitral insufficiency
Case 3			
Mother: 22 years of age, G3P1A1, biamniotic bichorionic twin pregnancy, 23 weeks of gestation, girl 400 g, boy 435 g, both died during labour		Mother: 23 years of age, G4P2-1A1, 20 weeks of gestation, girl, 220 g	
Cause of death	Prematurity; PPROM since 19 weeks of gestation	Cause of death	Prematurity; PPROM since 20 weeks of gestation
Contributing factors	CIN III lesion treated with LETZ, twin pregnancy, chorioamnionitis, smoking (10 cigarettes/day)	Contributing factors	CIN III lesion treated with LETZ, smoking (5 cigarettes/day)
Comorbidities	Congenital heart disease with Mustard correction	Comorbidities	Congenital heart disease with Mustard correction
Case 4			
Mother: 34 years of age, G1P0, 17 weeks of gestation, girl, 310 g, died in utero		Mother: 36 years of age, G2P1-1, 21 weeks of gestation, girl, 330 g, died in utero	
Cause of death	Prematurity; PPROM since 17 weeks of gestation	Cause of death	Prematurity; PPROM since 20 weeks of gestation
Contributing factor	Chorioamnionitis	Contributing factors	Chorioamnionitis, umbilical cord prolapse
Comorbidities	Leiomyoma, endometriosis	Comorbidities	Leiomyoma, endometriosis
Case 5			
Mother: 32 years of age, G2P1, monoamniotic monochorionic twin pregnancy, TRAP sequence requiring laser therapy. Foetus I: acardiac foetus died during laser therapy; foetus II: 25 weeks of gestation, boy, 745 g, died in utero (3 weeks after laser therapy)		Mother: 34 years of age, G3P2-1, monoamniotic monochorionic twin pregnancy, foetus 1: boy, 135 g, died in utero at 17 weeks of gestation; foetus II: boy, 970 g, died in utero at 30 weeks of gestation	
Cause of death	Placenta; placental pathology; development	Cause of death foetus I	Unknown, despite thorough investigation
		Cause of death foetus II	Placenta; placental pathology, development
Contributing factors	Monoamniotic monochorionic twin pregnancy, TRAP sequence, IUGR	Contributing factors	Monoamniotic monochorionic twin, IUGR, oligohydramnion
Comorbidities	None	Comorbidities	None
Case 6			
Mother: 24 years of age, G2P1, 27 weeks of gestation, girl, 780 g, died in utero		Mother: 25 years of age, G3P2-1, 30 weeks of gestation, girl, 1010 g, died in utero	
Cause of death	Prematurity; preterm labour	Cause of death	Placenta; placental bed pathology
Contributing factor	Cardiocirculatory insufficiency due to nifidipine-induced hypotension	Contributing factors	None
Comorbidities	None	Comorbidities	None
Case 7			
Mother: 24 years of age, G1P0, 24 weeks of gestation, girl, 685 g, died in utero		Mother: 26 years of age, G2P1-1, 20 weeks of gestation, boy, 340 g, died during labour	
Cause of death	Placenta; placenta bed pathology	Cause of death	Prematurity; preterm labour
Contributing factors	HELLP syndrome, pre-eclampsia, obesity (BMI 39)	Contributing factor	Obesity (BMI 40)
Comorbidities	Heterozygous factor V Leiden mutation	Comorbidities	Heterozygous factor V Leiden mutation

IUGR: intrauterine growth restriction; PPROM: preterm prelabour rupture of membranes; LETZ: loop electrosection of the transformation zone; TRAP: twin reversed arterial perfusion; BMI: body mass index; CIN: cervical intra-epithelial neoplasia.

Table 4
Recurrent foetal death after unexplained cause of death in the index pregnancy classified according to the Tulip classification.

Index pregnancy		Subsequent pregnancy	
Case 8			
Mother: 37 years of age, G5P4, 18 weeks of gestation, boy, 50 g, died in utero		Mother: 38 years of age, G6P5-1, 21 weeks of gestation, girl, 135 g, died in utero	
Cause of death	Unknown; despite thorough investigation	Cause of death	Unknown; despite thorough investigation
Contributing factor	Age of mother	Contributing factor	Age of mother
Comorbidities	None	Comorbidities	None
Case 9			
Mother: 33 years of age, G5P4, 27 weeks of gestation, girl, 155 g, died in utero		Mother: 33 years of age, G6P5-1, 18 weeks of gestation, boy, 50 g, died in utero	
Cause of death	Unknown; despite thorough investigation	Cause of death	Unknown; despite thorough investigation
Contributing factor	Obesity (BMI 30)	Contributing factor	Obesity (BMI 30)
Comorbidities	None	Comorbidities	None
Case 10			
Mother: 40 years of age, G3P1A1, 19 weeks of gestation, girl, 45 g, died in utero		Mother: 41 years of age, G4P2-1A1, 23 weeks of gestation, girl, 460 g, died during labour	
Cause of death	Unknown; despite thorough investigation	Cause of death	Congenital anomaly; chromosomal defect; numerical (trisomy 18)
Contributing factor	Age of mother	Contributing factor	Age of mother
Comorbidity	Leiomyoma	Comorbidity	Leiomyoma
Case 11			
Mother: 40 years of age, G6P5-2, 20 weeks of gestation, boy, 240 g, died in utero		Mother: 41 years of age, G7P5-3, 29 weeks of gestation, boy, 1500 g, died in utero	
Cause of death	Unknown; important information missing	Cause of death	Placenta; placental bed pathology: placental abruption
Contributing factors	Age of mother, hyperhomocysteinaemia	Contributing factors	Age of mother, hyperhomocysteinaemia
Comorbidities	None	Comorbidities	None

BMI: body mass index.

3. Results

The authors identified 193 women with a foetal death beyond 16 weeks of gestation in the perinatal database. Thirty women who could not be traced due to a change in address or who did not give permission for use of their medical records after the index pregnancy were excluded. The excluded women were comparable to the study group in terms of age, parity and cause of death in the index pregnancy. Medical records for 163 women were reviewed. Table 1 shows the cause of death in the index pregnancy classified by the Tulip classification. Contributing factors and comorbidities were known for all index pregnancies.

Table 2 shows the pregnancy outcome after the index pregnancy, categorized by cause of death in the index pregnancy. Out of 163 women, 119 women (73.0%) had a subsequent ongoing pregnancy beyond 16 weeks of gestation, including six twin pregnancies (5.0%). For 16 women (9.8%), the subsequent pregnancy resulted in a miscarriage before 16 weeks of pregnancy. Twenty-eight women (17.2%) abstained from pregnancy.

Six of the subsequent pregnancies ended in foetal death between 17 and 22 weeks of gestation, and five of the subsequent pregnancies resulted in foetal death beyond 22 weeks of gestation. In one twin pregnancy, one foetal death occurred in early gestation and one foetal death occurred beyond 22 weeks of gestation. These 11 pregnancies (including one twin pregnancy) were also classified according to the Tulip classification including cause of death, contributing risk factors and comorbidities.

The cause of death in the index pregnancy was explained in seven cases. Table 3 shows the cause of death in these seven cases in comparison with the cause of death in the subsequent pregnancy. Table 4 shows the results for both the index pregnancy and the subsequent pregnancy for the four cases where the cause of death in the index pregnancy was unexplained. Contributing factors are described.

4. Comment

There is no international consensus regarding which system should be used for classification of perinatal mortality. Since 1954, more than 30 classification systems for perinatal mortality have been introduced [17]. The Tulip classification was used in this study; this system was designed using a pathophysiological background to identify the unique initial demonstrable entity on the causal pathway to death for the purposes of counselling and prevention [15]. The proportion of unexplained stillbirths depends on which classification system is used, varying from 9.5% up to 50.2%. In comparison with other classification systems, the Tulip classification has been shown to have the best inter-rater agreement and a low proportion of unexplained stillbirths [17]. Risk factors are described as contributing factors. In the literature, known risk factors for perinatal mortality are maternal comorbidities (hypertension, diabetes), advanced maternal age, smoking, obesity and multiple gestation [14,18–23]. The use of different classification systems for foetal death limits the possibility for meaningful comparisons between countries regarding causes of foetal death.

Due to underlying risk factors and causes, a history of foetal death poses a risk for adverse pregnancy outcome in subsequent pregnancies with an increased rate of complications and foetal death. Black et al. performed a retrospective study including 364 women, and found no increased incidence of stillbirth (after 20 weeks of gestation) compared with a control group following adjustment for pre-eclampsia, abruption, preterm delivery and low birth weight [10]. In this study, 44% of all stillbirths were unexplained. Lurie et al. reported a favourable pregnancy outcome following stillbirth in a cohort of 54 women [11]. In contrast, Sharma et al. suggested that a history of foetal death beyond 20 weeks of gestation was associated with an almost six times higher risk of recurrence (hazard ratio 5.8, 95% confidence interval 3.7–9.0) [13]. However, the cause of death in subsequent pregnancies was often not described clearly in these studies, and the risk of recurrent foetal death was estimated for all causes of death together. For the purposes of counselling and prevention, determination of the cause of death and risk factors for a previous foetal death is essential. No previous studies have described recurrent foetal death using a comparison of the cause of death in the index pregnancy and the cause of death in the subsequent pregnancy, both classified using a validated classification system.

As such, this study reported the cause of death in cases of recurrent foetal death according to the Tulip classification. In the authors' tertiary referral centre, foetal deaths between 16 and 22 weeks of gestation are registered and the cause of death is classified in the same way as late stillbirths; this differs from other registration systems. The most common cause of death in the index pregnancies in this study was placental (78/163, 47.8%). The variations in cause of death in the index pregnancy (Table 1) were comparable to the findings of other studies using the Tulip classification, which also found that a placental cause of death was most common [25,26].

Out of 163 women, 28 women (17.2%) did not become pregnant again after their index pregnancy (Table 2). Unfortunately, it is not known whether this was due to general anxiety, no desire to become pregnant again or problems with conception.

Out of 11 cases of recurrent foetal death, the causes of death were explained for the index pregnancy and the subsequent pregnancy in seven cases (Table 3). Cause-specific recurrence of foetal death was caused by placental pathology and prematurity (Cases 1–4). In Case 1, the cause of death in both pregnancies was ascribed to placental abruption without signs of massive infarction, known to have a recurrence risk of 9–15% [1,24]. A contributing risk factor was smoking. Placental pathology originated during development of the placenta itself, abnormalities in the parenchyma or localization of the placenta. Case 2 was an example of an acquired placenta parenchyma disorder of the villi and intervillous space. The cause of recurrent foetal death in Case 2 was massive perivillous fibrin deposition (MPFD) in a woman with systemic sclerosis. Recurrent adverse pregnancy outcome in systemic sclerosis is well known, and miscarriages, foetal death and premature births are common, partly due to placental pathology, including MPFD [27]. After a pregnancy that was complicated by PPROM, the risk of recurrence is increased 20-fold and the risk of recurrent preterm delivery is increased almost four-fold [28]. In two cases (Cases 3 and 4), the cause of death was explained by recurrent PPROM which initiated preterm delivery. Pathological placental examination showed signs of chorioamnionitis, intervillositis and deciduitis. There were no clinical signs of intra-uterine infection. Contributing risk factors in Case 3 were a twin pregnancy (index pregnancy) and history of a loop electrosection of the transformation zone because of a cervical intraepithelial neoplasia III lesion. In Case 5, the index pregnancy and the subsequent pregnancy were spontaneous monoamniotic monochorionic twin pregnancies ending in two stillbirths; the cause of death was non-optimal placental development. Contributing factors were twin pregnancy and intra-uterine foetal growth restriction. The risk of foetal death in monoamniotic twin pregnancy in the Dutch population is 19% [29]. It is very rare to have a spontaneous monoamniotic pregnancy twice. In Cases 6 and 7, the cause of death differed between the index pregnancy and the subsequent pregnancy: preterm labour vs. placental bed pathology. Placental bed pathology is known to be associated with preterm delivery [30], but this could not be confirmed on placental examination in Case 6 and death in both pregnancies was classified differently. In Case 7, the placenta of the index pregnancy was not submitted for examination.

In three cases, the cause of death in the index pregnancy was unexplained despite thorough investigation; placental examination and autopsy were performed (Table 4). In Cases 8 and 9, the cause of the subsequent foetal death was also unknown. The only known contributing risk factors were the age of the mother and obesity. In Case 10, there was no clear relationship between the causes of death in the two pregnancies; cytogenetic analyses in the index pregnancy showed a normal karoytype. In Case 11, the cause of death in the index pregnancy was unexplained because important information was missing; neither placental examination nor autopsy were not performed. As the cause of the subsequent foetal death was placental bed pathology, the lack of examination of the placenta in the index pregnancy was a missed opportunity for the parents to have more specific counselling.

The results show an association between the cause of death in the index pregnancy and the cause of death in the subsequent pregnancy in half of the cases, especially in early gestation. This illustrates the importance of registration and classification of foetal losses at early gestation, which is often underestimated in reporting systems [2]. Unfortunately, due to the small population size, the risk of recurrent foetal death with the same cause as the index pregnancy could not be established.

In summary, this study shows various causes of foetal death. There seems to be a relationship between the cause of death in the index pregnancy and the cause of death in the subsequent pregnancy, especially in early gestation. It is important to identify the cause of death to enable the parents to receive more appropriate counselling about risk in a subsequent pregnancy, and to institute preventive strategies to reduce the risk of foetal death. Before preventive strategies can be instituted and implemented to reduce the risk of foetal death, the causes and mechanisms of antepartum death, risk factors related to the cause of death and the risk of recurrence need to be well defined. Obligate investigations include autopsy and placental examination.

This study illustrates that using a validated classification system for recurrent foetal death, where both deaths were classified in the same way, provides more insight into pathophysiological pathways leading to foetal death. This will aid understanding of foetal death and enable meaningful comparisons to be made in cases of recurrent foetal death. Identification and registration of the cause of death in early gestation is essential for further research. In this way, more research can be performed studying the origin of these causes and may provide more preventive strategies.

A limitation of this study is that the study population was small. A large population-based study is necessary to confirm cause-related recurrent foetal death and to establish the risk of recurrence.

Conflict of interest statement

None declared.

Ethical approval

The study was approved by the Medical Ethics Committee of the University Medical Centre Groningen, and all women gave informed consent.

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